

Protocol Title: *"Clinical Protocol for Modification of Oncogene and Tumor Suppressor Gene Expression in Non-Small Cell Lung Cancer (NSCLC)"*

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The purpose of this protocol is to study a way of stopping cancer causing genes from functioning in human lung cancer cells in patients. Two types of cancer causing genes have been identified in human lung cancer. One of these genes is the K-ras oncogene. A mutation in a single base causes this gene to produce an abnormal protein which changes the cell from normal to malignant. A second gene that is altered in human lung cancer is the p53 tumor suppressor gene. A mutation or deletion of both copies of this gene causes the cell to become cancerous.

This protocol uses a gene therapy technique to turn off production of the abnormal K-ras protein and to replace the normal function of the p53 gene. DNA that produces "antisense" (mirror image) RNA is introduced into the cancer cell. This antisense RNA is specifically targeted to the RNA (sense) that is producing the abnormal K-ras protein. The sense and antisense RNAs bind together and this prevents the abnormal K-ras protein from being produced. The normal p53 gene will be introduced into lung cancer cells. This normal gene will overcome the function of the mutant gene and also replace the normal p53 function.

A novel feature of this protocol is that the genes will be introduced into human cancer cells in the patient by a retrovirus. A special retrovirus that is harmless to patients and rendered incapable of dividing is used. The antisense K-ras and the p53 gene are each inserted separately in this retrovirus. The retrovirus is taken up by the cancer cell and integrated into the cancer cell's DNA where the newly inserted gene is now expressed. Constant expression of these genes renders the cancer cell incapable of growing and dividing. Only dividing cells such as cancer cells can incorporate the retrovirus. Thus, this therapy is very selective for cancer cells. The antisense K-ras gene and the normal p53 gene are not harmful to normal cells. The retrovirus will be injected directly into the lung cancer.

Patients with lung cancer who are unable to have surgery, radiation therapy, or chemotherapy may participate. Patients must have a cancer that can be reached with the bronchoscope and that is obstructing air passage to the lung. Patients will have some of the tumor removed. The tumor will be tested to determine if it has one or the other genetic abnormality. The retrovirus capable of correcting the specific gene abnormality will be directly injected into the tumor. Following this the growth of the tumor will be measured. Patients may have multiple injections of the retrovirus. The tumor will also be studied to determine if the tumor cells are taking up the retrovirus.